

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number
WO 2004/082525 A2

(51) International Patent Classification⁷:

A61F

(21) International Application Number:

PCT/US2004/007828

(22) International Filing Date: 12 March 2004 (12.03.2004)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/454,918

14 March 2003 (14.03.2003) US

(71) Applicant (for all designated States except US):
SINEXUS INC. [US/US]; 10240 Bubb Road, Cupertino,
CA 95014 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): EATON, Donald,
J. [US/US]; 335 Kings Mountain Road, Woodside, CA
94062 (US). MORAN, Mary, L. [US/US]; 2973 Woodside
Road, Woodside, CA 94062 (US). BRENNEMAN, Rod-
ney [US/US]; 34002 Las Palmas Del Mar, San Juan Capis-
trano, CA 92675 (US).

(74) Agents: AMII, Lisa, A. et al.; Morrison & Foerster LLP,
755 Page Mill Road, Palo Alto, CA 94304 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SINUS DELIVERY OF SUSTAINED RELEASE THERAPEUTICS

(57) Abstract: The invention provides biodegradable implants for treating sinusitis. The biodegradable implants have a size, shape, density, viscosity, and/or mucoadhesiveness that prevents them from being substantially cleared by the mucociliary lining of the sinuses during the intended treatment period. The biodegradable implants include a sustained release therapeutic, e.g., an antibiotic, a steroidal anti-inflammatory agent, or both. The biodegradable implants may take various forms, such as rods, pellets, beads, strips, or microparticles, and may be delivered into a sinus in various pharmaceutically acceptable carriers.

WO 2004/082525 A2

SINUS DELIVERY OF SUSTAINED RELEASE THERAPEUTICS

RELATED APPLICATIONS

This application claims priority from U.S. Application Serial No. 60/454,918, filed March 14, 2003.

FIELD OF THE INVENTION

[0001] This invention relates to biodegradable implants and methods for placing one or more of these implants into a paranasal sinus. The implants provide local sustained release of a therapeutic agent for the prophylaxis or treatment of sinusitis. Included in the description are implants delivered in such various forms as pellets, rods, strips, and microparticles.

BACKGROUND OF THE INVENTION

[0002] The paranasal sinuses are air-filled cavities within the facial skeleton. Each paranasal sinus is contiguous with a nasal cavity and drains into the nose through a sinus ostium. Although other factors may be involved, the development of sinusitis (inflammation of the mucosal lining of the sinuses) is most often attributed to blockage of one or more of these sinus ostia, followed by mucostasis and microbial overgrowth in the sinus cavity. Ostial blockage may stem from predisposing anatomical factors, or inflammation and edema of the mucous lining in the area of the ostia, arising from such etiologies as viral or bacterial upper respiratory infection or chronic allergic processes.

[0003] Traditionally, sinusitis has been medically managed by the oral administration of antibiotics and steroids. However, penetration of these systemically delivered agents into the sinus mucosa is limited due to poor blood flow to the sinuses. Therapeutic agents contained in aqueous solutions, creams, or gels, for topical application in the nose have also been formulated, but usually never travel far enough into the nose to reach the sinuses, are blocked from entering the sinuses due to obstructed ostia, or have such short contact with the sinus mucosa that absorption of the agent is low. For similar reasons, nasally

inhaled steroid and anti-infective aerosols that have been developed to treat sinusitis are equally ineffective.

[0004] The delivery of ampicillin from a poly(lactic-co-glycolic)acid (PLGA) film to increase residence time of the antibiotic in rabbit sinuses has been investigated for the treatment of sinusitis (Min et al. Mucociliary Activity and Histopathology of Sinus Mucosa in Experimental Maxillary Sinusitis: A Comparison of Systemic Administration of Antibiotic and Antibiotic Delivery by Polylactic Acid Polymer. *Laryngoscope* 105:835-342 (1995) and Min et al. Application of Polylactic Acid Polymer in the Treatment of Acute Maxillary Sinusitis in Rabbits. *Acta Otolaryngol* 115:548-552 (1995)). Although clinical signs of sinusitis improved, the procedure for placing the film required that a hole be drilled through the anterior wall of the maxillary sinus.

[0005] Consequently, a biodegradable implant for administering a sustained release therapeutic agent to the paranasal sinuses for a prolonged time period without being substantially cleared by the mucociliary lining of the sinuses, and methods for delivering the implant in a minimally invasive fashion may provide significant medical benefit for patients afflicted with sinusitis.

SUMMARY OF THE INVENTION

[0006] The present invention is a biodegradable implant for treating sinusitis that includes a sustained release therapeutic agent dispersed within a biodegradable matrix, and which has at least one characteristic that substantially prevents clearance of the implant from the sinus by its mucociliary layer during the intended treatment period after delivery of the implant into the sinus. Characteristics such as size, shape, density, viscosity, mucoadhesiveness, or a combination thereof may be altered to substantially prevent this clearance.

[0007] The biodegradable implant may include various therapeutic agents, including, but not limited to, anti-infective agents, anti-inflammatory agents, and combinations thereof. Examples of anti-infective agents include antibacterial agents, antifungal agents, antiviral agents, and antiseptics. The anti-inflammatory agent may be a nonsteroidal anti-inflammatory agent or a steroidal anti-

inflammatory agent. In a preferred variation, steroidal anti-inflammatory agents are used.

[0008] The matrix of the implant may be made from any biodegradable and biocompatible polymer, including such polymers as mucoadhesive polymers, poly(ortho esters), and poly(lactic-co-glycolic)acid (PLGA) copolymer. The biodegradable polymer matrix may also be formed as a rod, pellet, bead, strip, or microparticle, and placed in a pharmaceutically acceptable carrier if desired. When the biodegradable implant is a microparticle, usually a plurality of microparticles are delivered into the sinus to treat sinusitis. The microparticles may or may not be porous, and may have an average diameter of between about 0.1-500 μm , between about 0.1-100 μm , between about 0.1-50 μm , or between about 0.1-10 μm . In some instances, the form of the biodegradable implant may change after delivery into the sinus. For example, a poly(ortho ester) implant in the form of a strip having a series of predetermined fracture lines or zones may fracture into a plurality of smaller segments as it degrades along the fracture lines in the sinus.

[0009] The biodegradable implant may deliver a sustained release therapeutic agent over at least about one week, over at least about two weeks, over at least about three weeks, over at least about four weeks, over at least about six weeks, over at least about two months, or over at least about three months. In a preferred variation, the sustained release therapeutic agent is delivered into the sinus over about three weeks.

[0010] The biodegradable implants may be delivered into a sinus using devices of various designs, but at least which include a pusher and a conduit, e.g., a catheter, needle, or angiocatheter. For example, the pusher and/or conduit may be made such that they are variably stiff along their lengths. In addition, the opening in the conduit through which the implant is delivered may be positioned in the conduit side wall or at the tip. Furthermore, the distal portion of the conduit may be angulated to facilitate access of the sinus ostium if indicated. In one variation, the distal portion is malleable such that the physician may angulate the conduit themselves just prior to accessing the sinus ostium.

[0011] The biodegradable implants and devices for their deployment may be used in a system for treating sinusitis. In general, the system works by first placing the conduit having one or more implants within its lumen either through a sinus ostium or a sinus wall. A pusher within the lumen of the conduit is then distally advanced to slidably engage the implant(s) and move it through an opening in the distal portion of the conduit into the sinus. The opening may be in the conduit side wall or tip. Usually, the conduit will be preloaded with one or more implants. In some instances, a tool for visualizing the sinus ostium or sinus wall is desired. Examples of such tools include endoscopes and computed tomography (CT) scanners.

[0012] The biodegradable implants may also be used for reducing inflammation from a sinus procedure. These implants would also include a sustained release therapeutic agent dispersed within a biodegradable matrix and have at least one characteristic that substantially prevents clearance of the implants from a sinus during a treatment period after delivery of the implant into the sinus. The treatment period may be of any duration which the physician deems is suitable to reduce the inflammation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figures 1A-1B are cross-sectional views of the distal portion of an implant delivery device. In Figure 1A, the biodegradable implant is delivered through a side opening in the conduit. In Figure 1B, the biodegradable implant is delivered through the tip of the conduit.

[0014] Figure 2A is a cross-sectional view of a distal portion of a multiple implant delivery device.

[0015] Figure 2B is a cross-sectional view of a handle that may be coupled to the distal portion of the multiple implant delivery device shown in Figure 2A.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The biodegradable implants of this invention may take various forms, but are generally designed to have a size and shape appropriate for the

intended method of delivery, e.g., through the sinus ostium or by puncture through a sinus wall, and a density, viscosity, and/or mucoadhesiveness such that the implant is not substantially cleared from the sinus over the duration of treatment. Once within the sinus, the implant releases a therapeutic agent over a prolonged time period, for example, over at least one week, over at least two weeks, over at least three weeks, or over at least four weeks or more, to treat sinusitis.

Definitions

[0017] For purposes of this description, we use the following terms as defined in this section, unless the context of the word indicates a different meaning.

[0018] By “sinus” it is meant all sinuses, i.e., the maxillary, ethmoid, frontal, and sphenoidal sinuses.

[0019] By “subject” it is meant mammalian subjects, preferably humans. Mammals include, but are not limited to, primates, farm animals, sport animals, cats, dogs, rabbits, mice, and rats.

[0020] As used herein, the term “treat”, “treating”, or “treatment” refers to the resolution, reduction, or prevention of sinusitis or the sequelae of sinusitis.

[0021] As used herein, the term “therapeutic agent”, “active agent”, and “drug” are used interchangeably and refer to any substance used to treat sinusitis.

[0022] By “therapeutic amount” it is meant a concentration of therapeutic agent that has been locally delivered to a sinus that is appropriate to safely treat sinusitis.

Biodegradable Implants

[0023] The implants of this invention generally include a therapeutic agent dispersed within a biodegradable polymer. The therapeutic agent may be homogeneously or inhomogeneously dispersed throughout the implant. Implant compositions may vary, depending, for example, on the particular therapeutic agent employed, duration of desired drug release, type of sinusitis being treated,

and medical history of the patient. However, in all instances, the biodegradable implant is formulated for sustained release of the therapeutic agent.

Therapeutic agents

[0024] The therapeutic agents that may be used in the biodegradable implants include, but are not limited to, anti-infective agents, anti-inflammatory agents, or a combination thereof. Anti-infective agents generally include antibacterial agents, antifungal agents, antiviral agents, and antiseptics. Anti-inflammatory agents generally include steroidal and nonsteroidal anti-inflammatory agents.

[0025] Examples of antibacterial agents that may be incorporated in the biodegradable implants include aminoglycosides, amphenicols, ansamycins, β -lactams, lincosamides, macrolides, nitrofurans, quinolones, sulfonamides, sulfones, tetracyclines, and any of their derivatives. In one variation, β -lactams are the preferred antibacterial agents.

[0026] β -lactams that may be included in the implants include carbacephems, carbapenems, cephalosporins, cephamycins, monobactams, oxacephems, penicillins, and any of their derivatives. In one variation, penicillins (and their corresponding salts) are the preferred β -lactams.

[0027] The penicillins that may be used in the biodegradable implants include amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin G benethamine, penicillin G benzathine, penicillin G benzhydrylamine, penicillin G calcium, penicillin G hydrabamine, penicillin G potassium, penicillin G procaine, penicillin N, penicillin O, penicillin V, penicillin V benzathine, penicillin V hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, and ticarcillin. In

one variation, amoxicillin may be included in the biodegradable implant. In another variation, the biodegradable implant includes ampicillin. Penicillins combined with clavulanic acid such as Augmentin® (amoxicillin and clavulanic acid) may also be used.

[0028] Examples of antifungal agents that may be used in the biodegradable implants include allylamines, imidazoles, polyenes, thiocarbamates, triazoles, and any of their derivatives. In one variation, imidazoles are the preferred antifungal agents.

[0029] Typically, if inclusion of an anti-inflammatory agent is desired, a steroidal anti-inflammatory agent, e.g., a corticosteroid, is employed. Examples of steroidal anti-inflammatory agents that may be used in the implants include 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortol, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and any of their derivatives. In one variation, budesonide is included in the implant as the steroidal anti-inflammatory agent. In another variation, the steroidal anti-inflammatory agent may be mometasone furoate. In yet another variation, the steroidal anti-inflammatory agent may be beclomethasone.

[0030] The therapeutic agent may constitute from about 5% to about 90%, about 15% to about 75%, or about 30% to about 60% by weight of the implant. The amount of therapeutic agent used will usually depend on factors such as the particular agent incorporated, the suspected etiology of the sinusitis, and the severity of clinical symptoms, but in all instances will usually be an amount that is therapeutic upon delivery into a sinus. Ancillary agents such as topical decongestants may also be included.

Polymer Matrix

[0031] Selection of the biodegradable polymer matrix to be employed will vary depending on the residence time and release kinetics desired, method of implant delivery, particular therapeutic agent used, and the like. An exemplary list of biodegradable polymers that may be used are described in Heller, Biodegradable Polymers in Controlled Drug Delivery, In: "CRC Critical Reviews in Therapeutic Drug Carrier Systems", Vol. 1. CRC Press, Boca Raton, FL (1987). In all instances, the polymer matrix when degraded results in physiologically acceptable degradation products. The biodegradable polymer matrix may constitute at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% by weight of the implant.

[0032] In one variation, adhesiveness of the polymer matrix to the sinus mucosa is particularly desired. Mucoadhesive polymers are typically hydrophilic, and upon moistening, swell and become adhesive. Examples of mucoadhesive polymers that may be employed in the biodegradable implants include homopolymers of acrylic acid monomers such as polyacrylic acid and any of its pharmaceutically acceptable salts; copolymers of acrylic acid and methacrylic acid, styrene, or vinyl ethers; vinyl polymers such as polyhydroxyethyl acrylate, polyhydroxyethyl methacrylate, polyvinyl alcohol, and polyvinyl pyrrolidone; cellulosic derivatives such as methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and

carboxymethyl cellulose; polysaccharides such as alginic acid, sodium alginate, and tragacanth gum; collagen; gelatin; and any combination thereof.

[0033] In another variation, the biodegradable matrix is made from an orthoester, alone or in combination with other monomers. In a preferred variation, a poly(ortho ester) is used to constitute the polymer matrix.

[0034] In yet a further variation, polymers of hydroxyaliphatic carboxylic acids, either homo- or copolymers, are used to form the matrix. For example, polyesters including homo- or copolymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, caprolactone, and combinations thereof may be used. Copolymers of glycolic and lactic acid are of particular interest, where the rate of biodegradation is controlled by the ratio of glycolic to lactic acid. The percent of each monomer in poly(lactic-co-glycolic)acid (PLGA) copolymer may be 0-100%, about 20-80%, about 30-70%, or about 40-60%. In a preferred variation, a 50/50 PLGA copolymer is used.

[0035] In one variation, PLGA may be combined with budesonide to form the biodegradable sinus implant. In another variation, PLGA may be combined with mometasone furoate. If inclusion of an antibacterial agent is desired in the PLGA matrix, alone or in combination with a steroidal anti-inflammatory agent, Augmentin® may be used. If first-line antimicrobial therapy fails, or for penicillin allergy, a cephalosporin such as ciprofloxacin or macrolide such as erythromycin may be used in the PLGA matrix.

[0036] The biodegradable implants may be solid or semisolid and take a variety of suitable forms, such as rods or approximately spherical or rectangular pellets, beads, strips, or microparticles, so long as their size and shape is compatible with the selected sinus of implantation, and so long as the implants exhibit the desired release kinetics and deliver an amount of drug therapeutic for the intended type of sinusitis. In one variation, the implant is a rod having a length of about 1 mm to about 10 mm and a diameter of about 0.05 mm to about 5 mm. In another variation, the implant is a rod having a length of about 4 mm and a diameter of about 2 mm. In yet a further variation, the implant is a microparticle. When treating sinusitis, a plurality of these microparticles with or

without a carrier are delivered into the sinus. The microparticles may or may not be porous, and may have an average diameter of between about 0.1-500 μm , between about 0.1-100 μm , between about 0.1-50 μm , between about 0.1-10 μm , between about 0.1-1 μm , or between about 0.1-0.5 μm .

[0037] Also important is that the implant remain in the sinus during the intended period of drug delivery. The sinuses are lined with a ciliated epithelium and a layer of mucus. The cilia beat continuously, causing the mucous layer to slowly flow out of the sinus toward the pharynx. Accordingly, in order to effectively treat sinusitis with an implant, the implant must typically remain in the sinus long enough to deliver a drug in a therapeutic amount. The biodegradable implants of this invention have a mucoadhesiveness, size, shape, viscosity, and/or density that allows a substantial amount of the implant to remain in the sinus during the intended period of drug delivery.

[0038] Furthermore, the implant may be of a design that allows it to take a form that is different after it is delivered into the sinus from that before delivery. For instance, an implant delivered into the sinus as a rod or strip having a series of predetermined fracture lines or zones may fracture into a plurality of smaller segments as it degrades along the fracture lines.

Additional Agents

[0039] The implants of this invention may further include components such as preservatives, buffers, binders, disintegrants, lubricants, and any other excipients necessary to maintain the structure and/or function of the implants. Furthermore, the implants may be placed in a pharmaceutically acceptable carrier, e.g., when the implants are microparticles, to form a suspension such as a semi-solid gel. Common gel bases include, but are not limited to, carbomer, liquid paraffin, water, glycerol, propylene glycol, hyaluronic acid or sodium hyaluronate, or a combination thereof. The types of gels that may be formed include, e.g., inorganic and organic gels, hydrogels, or organogels.

[0040] In addition to microparticle density, the viscosity of the gel may be adjusted to a level that allows delivery into the sinus and prevents substantial

clearance of the microparticles (implants) from the sinus. The gel may also be prepared in adhesive form (using adhesive polymers such as polyacrylic acid, sodium carboxymethyl cellulose, or polyvinylpyrrolidone) to increase the contact time of the therapeutic agent with the sinus mucosa.

Release Kinetics

[0041] In general, the implants of this invention are formulated with particles of a therapeutic agent dispersed within a biodegradable polymer matrix, and formulated to provide sustained-release of the therapeutic agent. If made from a non-swelling polymer, e.g., PLGA or poly(ortho ester), release of the active agent from the matrix is probably achieved by erosion of the biodegradable polymer matrix and by diffusion of the particulate therapeutic agent into the mucous layer of the sinus. Factors that may influence the release kinetics include such characteristics as the size of the drug particles, the solubility of the drug, the ratio of drug to polymer(s), the method of implant manufacture, the implant surface area exposed, and the erosion rate of the matrix polymer(s). In the case of polymer swelling, as seen with hydrogels, a therapeutic agent is released as liquid diffuses through exposed pathways in the implant.

[0042] The therapeutic agent may be released from the implant over a prolonged time period including, but not limited to, at least about one week, at least about two weeks, at least about three weeks, at least about four weeks, at least about 6 weeks, at least about two months, or at least about three months. In one variation, the therapeutic agent is released over about two weeks to about four weeks.

Delivery Device

[0043] The biodegradable implants may be placed into the sinus using various implant delivery devices. The device generally includes a conduit, e.g., a catheter, having an elongate pusher within its lumen. The conduit and pusher may be flexible or rigid, or may be designed to have varying degrees of stiffness along its length, e.g., the distal portion of the conduit may be stiffer than the proximal

portion. In addition, the distal portion of the conduit may be variously angulated to facilitate positioning and advancement of the conduit through the sinus ostium. For example, the distal portion may be angulated from about 0° to about 175°, from about 0° to about 135°, or from about 0° to about 90°.

[0044] The conduit may be made from any biocompatible material including, but not limited to, stainless steel and any of its alloys; titanium alloys, e.g., nickel-titanium alloys; polymers, e.g., polyethylene and copolymers thereof, polyethylene terephthalate or copolymers thereof, nylon, silicone, polyurethanes, fluoropolymers, poly (vinylchloride), and combinations thereof, depending on the amount of flexibility or stiffness desired. The pusher may be made from similar materials.

[0045] Usually, the device will be preloaded with a single implant within the lumen of the conduit, but more than one implant may be preloaded if desired. Once access through a sinus ostium has been obtained with the conduit, the pusher slidably engages the implant and is advanced until the implant exits the catheter into the sinus. An endoscope may also be used while positioning the conduit to aid with visualization of the ostium.

[0046] In certain cases, e.g., when ostia are closed or difficult to access, implant placement into one or more sinuses may be completed through the sinus wall using a sharp-tipped conduit, e.g., a needle, trocar, or angiocatheter, with or without visualization using computer image-guided technology or endoscopy. Once the appropriate access point for the sinus has been determined, force is applied to the sharp-tipped conduit so that it punctures the sinus wall. Advancement of a pusher through the conduit lumen then deposits an implant into the sinus.

[0047] Figures 1A-1B show examples of single implant delivery devices. The devices include an implant 10, a conduit 12 having a side wall 14, a lumen 16, a distal portion 18, an opening 20 in the distal portion 18, a tip 22, and a pusher 24. In Figure 1A, the conduit 12 includes a ramp 26 and an opening 20 positioned in the side wall 14. If delivering a solid implant, the opening will usually be approximately twice the diameter of the implant. The pusher 24 is

advanced distally within the lumen 16 to slidably engage the implant 10 and move it up the ramp 26 through the side wall 14 into the sinus. In Figure 1B, the opening 20 is positioned at the tip 22 of the conduit 12, and pusher 24 is advanced distally within the lumen 16 to slidably engage the implant 10 and move it through the tip 22. Although the conduit tips are shown to be blunt in the Figures, they may also be sharp and/or beveled, usually depending on the implant delivery method.

[0048] Figure 2A shows a device that delivers multiple implants. The device is similar to the single implant delivery device having a conduit 28 with a side wall 30, a lumen 32, a distal portion 34, an opening 36 in the distal portion 34, a tip 38, a pusher 40, and a ramp 42. Pusher 40 is distally advanced a preset distance to slidably engage the most proximal implant 44 within lumen 32. The pusher 40 is then further distally advanced a preset distance, e.g., a distance approximately equal to the length of one implant, to move the most distal implant 46 through opening 36 into the sinus.

[0049] A handle 48, as shown in Figure 2B, may be coupled to conduit 28 such that the handle lumen forms a continuous lumen with the lumen 32 of the conduit 28. The pusher 40 can then slide through this continuous lumen. The handle 48 further includes an injector 42, adjacent to and longitudinally aligned with the pusher 40, and a stepped slot 44 with various positions "O", "A", "B", and "C". Initially, when the injector 42 is pressed, the pusher 40 is distally advanced, and a key 46 coupled to the injector 42 moves the pusher 40 between positions "O" and "A". The distance between positions "O" and "A" is approximately equal to the length of the dispensed implant. Pusher 40 may then be rotated to move the key 46 from position "A" to position "B" in the stepped slot 44. Pressing the injector 42 again then moves the key along step "B" to position "C", and the pusher 40 a corresponding length to dispense another implant. Multiple implants may be delivered in this fashion, with the number of implants delivered depending on the number of steps in the stepped slot.

[0050] Although the various implant delivery devices described above deploy solid implants, this invention also contemplates the use of the devices to

deliver various semi-solid implants and gels into the sinus. A force applied to a predetermined amount of a semi-solid implant or gel composition in the conduit, e.g., by contact with a pusher or pressurized gas, could be used to deliver the implant or gel into the sinus.

Applications

[0051] The implants may be used to treat sinusitis affecting one or more of the maxillary sinus, the frontal sinus, the ethmoidal sinus, and the sphenoidal sinus.

[0052] Furthermore, the biodegradable implants may be used to treat acute or chronic sinusitis arising from predisposing anatomical conditions, chronic allergic processes, or conditions related to infection by various pathogens (e.g., bacteria, fungi, and viruses).

[0053] Examples of bacteria that may cause sinusitis include Alpha-hemolytic streptococci, Beta-hemolytic streptococci, Branhamella catarrhalis, Diptheroids, Haemophilis influenzae, Moraxella species, Pseudomonas aeruginosa, Pseudomonas maltophilia, Serratia marcescens, Staphylococcus aureus, and Streptococcus pneumoniae.

[0054] Examples of fungi that may cause sinusitis include Aspergillosis, Candida, Cryptococcus, Coccidioides, Histoplasma, and Mucor species.

[0055] The biodegradable implants may also be used to reduce inflammation resulting from a sinus procedure, typically, a sinus drainage procedure. Examples of sinus drainage procedures include, but are not limited to, widening/enlargement of a narrowed ostium, antral puncture and washout, and intranasal antrostomy. The implants may be delivered into a sinus using one of the methods previously described, usually after the procedure is completed, but they can also be delivered into a sinus before the procedure or during the procedure.

[0056] If enlarging an ostium, the affected sinus will generally be accessed through that enlarged ostium. The biodegradable implant(s) may then be deployed into the sinus via the enlarged ostium. With respect to antral puncture

and drainage or intranasal antrostomy, the affected sinus usually will be accessed at the antral puncture site or through the antrostomy. The biodegradable implant(s) will also usually be deployed into the sinus through the antral puncture site or antrostomy. However, if desired, the biodegradable implant(s) may be delivered through a natural ostium despite antral puncture or antrostomy being performed.

Method of Making the Implants

[0057] The method of preparing the implants of this invention will generally depend on the particular therapeutic agent or matrix polymer used, form of the implant, and the release kinetics desired, but may be made by any one of the numerous methods known in the art. For example, the implants may be made by such processes as compression, extrusion, molding, solvent evaporation, or solvent extraction.

* * *

All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, or patent application were specifically and individually indicated to be so incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and scope of the appended claims.

CLAIMS

1. A biodegradable implant for treating sinusitis comprising a sustained release therapeutic agent dispersed within a biodegradable matrix, wherein the biodegradable implant has at least one characteristic that substantially prevents clearance of the implant from a sinus during a treatment period after delivery of the implant into the sinus.
2. The biodegradable implant of claim 1 wherein the at least one characteristic is size of the implant.
3. The biodegradable implant of claim 1 wherein the at least one characteristic is shape of the implant.
4. The biodegradable implant of claim 1 wherein the at least one characteristic is density of the implant.
5. The biodegradable implant of claim 1 wherein the at least one characteristic is viscosity of the implant.
6. The biodegradable implant of claim 1 wherein the at least one characteristic is mucoadhesiveness of the implant.
7. The biodegradable implant of claim 1 wherein the sustained release therapeutic agent is selected from the group consisting of anti-infective agents, anti-inflammatory agents, and combinations thereof.
8. The biodegradable implant of claim 1 wherein the sustained released therapeutic agent comprises an anti-infective agent.

9. The biodegradable implant of claim 8 wherein the anti-infective agent is selected from the group consisting of antibacterial agents, antifungal agents, antiviral agents, and antiseptics.

10. The biodegradable implant of claim 8 wherein the anti-infective agent comprises an antibacterial agent.

11. The biodegradable implant of claim 10 wherein the antibacterial agent is selected from the group consisting of aminoglycosides, amphenicols, ansamycins, β -lactams, lincosamides, macrolides, nitrofurans, quinolones, sulfonamides, sulfones, tetracyclines, and any of their derivatives.

12. The biodegradable implant of claim 10 wherein the antibacterial agent comprises a β -lactam.

13. The biodegradable implant of claim 12 wherein the β -lactam comprises a penicillin.

14. The biodegradable implant of claim 13 wherein the penicillin comprises amoxicillin.

15. The biodegradable implant of claim 1 wherein the sustained release therapeutic agent is an anti-inflammatory agent.

16. The biodegradable implant of claim 15 wherein the anti-inflammatory agent is a nonsteroidal anti-inflammatory agent or a steroidal anti-inflammatory agent.

17. The biodegradable implant of claim 1 wherein the sustained release therapeutic agent comprises a steroidal anti-inflammatory agent.

18. The biodegradable implant of claim 17 wherein the steroidal anti-inflammatory agent is selected from the group consisting of 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and any of their derivatives.

19. The biodegradable implant of claim 18 wherein the steroidal anti-inflammatory agent comprises budesonide.

20. The biodegradable implant of claim 18 wherein the steroidal anti-inflammatory agent comprises mometasone furoate.

21. The biodegradable implant of claim 18 wherein the steroidal anti-inflammatory agent comprises beclomethasone.

22. The biodegradable implant of claim 1 wherein the biodegradable matrix is a biodegradable polymer matrix.

23. The biodegradable implant of claim 1 wherein the biodegradable matrix comprises a mucoadhesive polymer.

24. The biodegradable implant of claim 23 wherein the mucoadhesive polymer is selected from the group consisting of homopolymers of acrylic acid monomers and their pharmaceutically acceptable salts; copolymers of acrylic acid and methacrylic acid, styrene, or vinyl ethers; polyhydroxyethyl acrylate; polyhydroxyethyl methacrylate; polyvinyl alcohol; polyvinyl pyrrolidone; methyl cellulose; ethyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; carboxymethyl cellulose; alginic acid; sodium alginate; tragacanth gum; collagen; gelatin; and any combination thereof.

25. The biodegradable implant of claim 1 wherein the biodegradable matrix comprises poly(lactic-co-glycolic)acid (PLGA) copolymer.

26. The biodegradable implant of claim 25 wherein the sustained release therapeutic agent comprises amoxicillin.

27. The biodegradable implant of claim 25 wherein the sustained release therapeutic agent comprises budesonide.

28. The biodegradable implant of claim 25 wherein the sustained release therapeutic agent comprises mometasone furoate.

29. The biodegradable implant of claim 25 wherein the sustained release therapeutic agent comprises beclomethasone.

30. The biodegradable implant of claim 1 wherein the biodegradable matrix comprises a poly(ortho ester).

31. The biodegradable implant of claim 1 wherein the treatment period is about one week to about three months.

32. The biodegradable implant of claim 1 wherein the treatment period is about two weeks to about 4 weeks.

33. The biodegradable implant of claim 1 wherein the implant is of a form selected from the group consisting of rods, pellets, beads, strips, and microparticles.

34. The biodegradable implant of claim 1 wherein the implant is a microparticle.

35. The biodegradable implant of claim 34 in a pharmaceutically acceptable carrier.

36. The biodegradable implant of claim 35 wherein the pharmaceutically acceptable carrier is a semi-solid gel.

37. The biodegradable implant of claim 1 wherein the implant further comprises a series of predetermined fracture lines such that after delivery into the sinus, the implant fractures into a plurality of segments.

38. The biodegradable implant of claim 1 wherein the sinus is a maxillary sinus, a frontal sinus, an ethmoid sinus, or a sphenoidal sinus.

39. The biodegradable implant of claim 1 wherein the sinus is the maxillary sinus.

40. A biodegradable implant for reducing inflammation from a sinus procedure comprising a sustained release therapeutic agent dispersed within a

biodegradable matrix, wherein the biodegradable implant has at least one characteristic that substantially prevents clearance of the implant from a sinus during a treatment period after delivery of the implant into the sinus.

41. The biodegradable implant of claim 40 wherein the sinus procedure is a sinus drainage procedure.

42. The biodegradable implant of claim 40 wherein the sinus procedure enlarges a narrowed sinus ostium.

43. The biodegradable implant of claim 40 wherein the sinus procedure is antral puncture and washout.

44. The biodegradable implant of claim 40 wherein the sinus procedure is intranasal antrostomy.

45. The biodegradable implant of claim 40 wherein the biodegradable matrix is a biodegradable polymer matrix.

46. The biodegradable implant of claim 40 wherein the sustained release therapeutic agent is mometasone furoate.

47. A system for treating sinusitis comprising:

a) an implant delivery device, the implant delivery device comprising a conduit having a lumen, a distal portion, a side wall, a tip, and an opening in said distal portion; and a pusher within the lumen; and

b) one or more biodegradable implants in the lumen of the implant delivery device, the one or more biodegradable implants comprising a sustained release therapeutic agent dispersed within a biodegradable matrix and having at

least one characteristic that substantially prevents clearance of the one or more implants from a sinus during a treatment period after delivery of the one or more implants into the sinus,

wherein the one or more implants are delivered into the sinus by distally advancing the pusher to slidably engage the one or more implants and move the one or more implants through the opening in the distal portion of the conduit.

48. The system of claim 47 wherein the biodegradable matrix is a biodegradable polymer matrix.

49. The system of claim 47 wherein the distal portion of the conduit is angulated.

50. The system of claim 47 wherein the conduit is preloaded with a single implant.

51. The system of claim 47 wherein the conduit is preloaded with a plurality of implants.

52. The system of claim 47 further comprising a tool for visualizing the sinus ostium or sinus wall.

53. The system of claim 52 wherein the tool is an endoscope.

54. The system of claim 52 wherein the tool is a computed tomography scanner.

55. The system of claim 47 wherein the conduit is a needle.

56. The system of claim 47 wherein the conduit is a catheter.

57. The system of claim 47 wherein the conduit is malleable.

58. A method for delivering a biodegradable implant into a sinus comprising:

a) loading one or more biodegradable implants into a conduit having a lumen, a distal portion, a side wall, a tip, and an opening in the distal portion;

b) accessing a sinus with the conduit;

c) deploying the one or more biodegradable implants through the opening in the distal portion of the conduit into the sinus,

wherein the one or more biodegradable implants comprise a therapeutic amount of an active agent for the treatment of sinusitis.

59. The method of claim 58 wherein the step of accessing comprises placing the conduit through a sinus ostium.

60. The method of claim 58 wherein the step of accessing comprises placing the conduit through a sinus wall.

61. The method of claim 58 wherein the step of deploying comprises slidably engaging the one or more biodegradable implants with a pusher and advancing the pusher within the conduit lumen.

62. The method of claim 58 wherein the step of deploying comprises contacting the one or more biodegradable implants with a pressurized gas.

63. The method of claim 58 wherein the distal portion of the conduit is angulated.

64. The method of claim 58 wherein the conduit is sharp-tipped.

65. The method of claim 58 wherein the opening is located in the side wall of the conduit.

66. The method of claim 58 wherein the opening is located at the tip of the conduit.

67. The method of claim 58 wherein the biodegradable implant is a biodegradable polymeric implant.

68. A method for delivering a biodegradable implant into a sinus comprising:

- a) loading one or more biodegradable implants into a conduit having a lumen, a distal portion, a side wall, a tip, and an opening in the distal portion;
- b) accessing a sinus with the conduit;
- c) deploying the one or more biodegradable implants through the opening in the distal portion of the conduit into the sinus,

wherein the one or more biodegradable implants comprise a therapeutic amount of an active agent for the reduction of inflammation from a sinus procedure.

69. The method of claim 68 wherein the step of accessing comprises placing the conduit through a sinus ostium.

70. The method of claim 68 wherein the step of accessing comprises placing the conduit through a sinus wall.

71. The method of claim 68 wherein the biodegradable implant is a biodegradable polymeric implant.

72. The implant of claim 68 wherein the active agent comprises mometasone furoate.

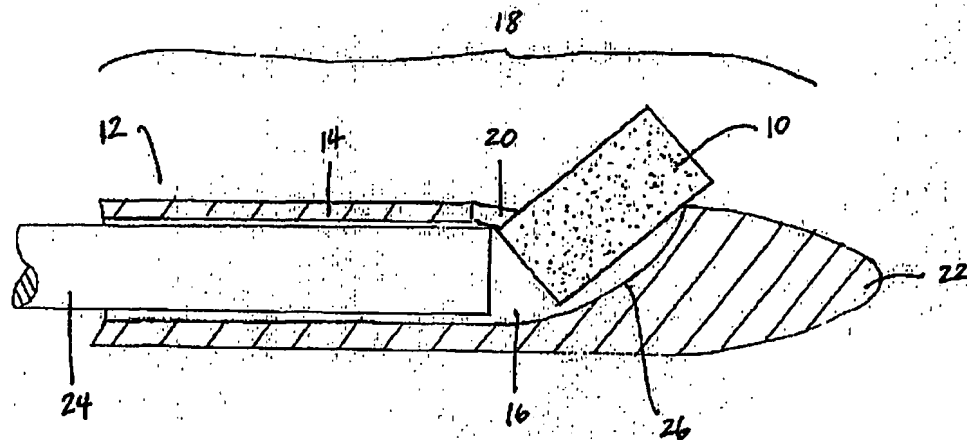


FIGURE 1A

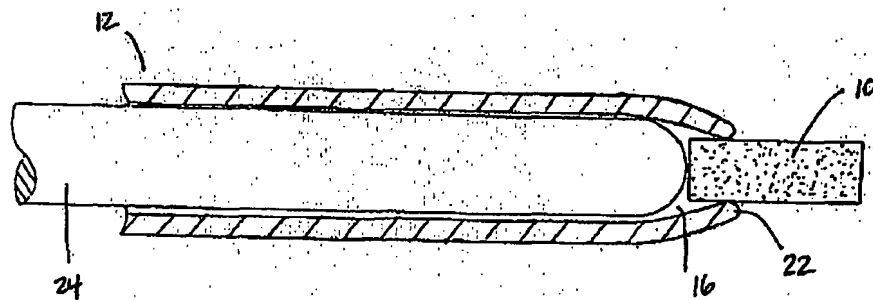


FIGURE 1B

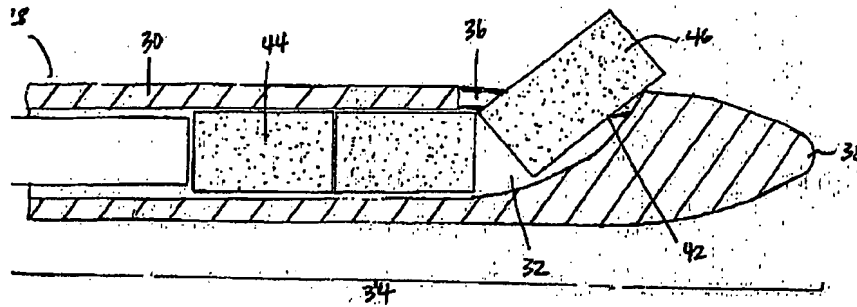


FIGURE 2A

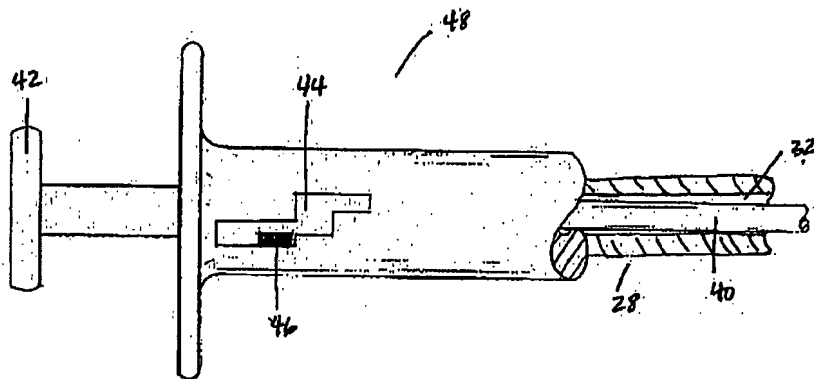


FIGURE 2B

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number
WO 2004/082525 A3

(51) International Patent Classification:
A61F 13/00 (2006.01)

(21) International Application Number:
PCT/US2004/007828

(22) International Filing Date: 12 March 2004 (12.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/454,918 14 March 2003 (14.03.2003) US

(71) Applicant (for all designated States except US):
SINEXUS, INC. [US/US]; 180 Farm Road, Wood-
side, CA 94062 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): EATON, Donald,
J. [US/US]; 335 Kings Mountain Road, Woodside, CA
94062 (US). MORAN, Mary, L. [US/US]; 2973 Woodside
Road, Woodside, CA 94062 (US). BRENNEMAN, Rod-
ney [US/US]; 34002 Las Palmas Del Mar, San Juan Capis-
trano, CA 92675 (US).

(74) Agents: AMII, Lisa, A. et al.; Morrison & Foerster LLP,
755 Page Mill Road, Palo Alto, CA 94304 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
13 April 2006

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SINUS DELIVERY OF SUSTAINED RELEASE THERAPEUTICS

(57) Abstract: The invention provides biodegradable implants for treating sinusitis. The biodegradable implants have a size, shape, density, viscosity, and/or mucoadhesiveness that prevents them from being substantially cleared by the mucociliary lining of the sinuses during the intended treatment period. The biodegradable implants include a sustained release therapeutic, e.g., an antibiotic, a steroidal anti-inflammatory agent, or both. The biodegradable implants may take various forms, such as rods, pellets, beads, strips, or microparticles, and may be delivered into a sinus in various pharmaceutically acceptable carriers.



WO 2004/082525 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/07828

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) : A61F 13/00 US CL : 424/422 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/422 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,054,122 A (MACPHEE et al) 25 April 2000 (25.04.200), see the whole document.	1-72
X	US 2002/0051793 A1 (DRABICK) 02 May 2002 (02.05.2002), paragraphs 7, 15, 16, 18-21, 27, 40, 42, 53 and claim 28.	1-72
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 21 January 2006 (21.01.2006)		Date of mailing of the international search report 24 FEB 2006
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201		Authorized officer: BLESSING FUBARA Telephone No. 571-272-1600